

Preface

Metabotropic glutamate (mGlu) receptors have been discovered in the mid-1980s by a French group of scientists (Sladeczek et al., *Nature*, 1985), who include some of the current leaders in the field. Since then, the field has grown exponentially, and now subtype-selective ligands of mGlu receptors [orthosteric agonists and antagonists, positive and negative allosteric modulators (PAMs and NAMs), and agonists/PAMs] are under development for the treatment of neurological and psychiatric disorders. The present book is the follow-up of the 8th International Meeting on Metabotropic Glutamate Receptors (Taormina, Italy, 2014) and incorporates chapters from some of the authorities in the mGlu receptor field.

The chapter by Philippe Rondard, Xavier Rovira, Cyril Goudet, and Jean-Philippe Pin is the state of the art of mechanisms regulating the structural and functional dynamics of mGlu receptors and their relevance to mGlu receptor pharmacology. This group of scientists has highly contributed to our current knowledge of physical interactions (homo- and heterodimerization) and allosteric modulation of mGlu receptors. Recent findings obtained by the authors and their collaborators lay the groundwork for the development of light-regulated ligands of mGlu receptors (i.e., drugs that can be either activated or inactivated by light). These molecules represent new valuable tools for the study of the role played by individual mGlu receptor subtypes in physiology and pathology with a high spatial and temporal resolution. Some of these drugs have recently appeared in the literature and hold promise for the treatment of pain and anxiety.

The chapter by Hardy Hagera and Denise Manahan-Vaughan is an excellent synopsis of the role played by mGlu receptors in mechanisms of hippocampal synaptic plasticity underlying information processing and long-term memory. This is a theme of great relevance from a therapeutic standpoint considering that some mGlu receptor ligands (e.g., mGlu5 receptor PAMs and mGlu2 receptor NAMs) are under development as cognition enhancers. In vivo studies on synaptic plasticity performed in Denise's lab are milestones in the mGlu receptor field.

The chapter by Zhengping Jia and Graham Collingridge focuses on mechanisms underlying mGlu receptor-dependent long-term depression (LTD) of excitatory synaptic transmission, a particular form of activity-dependent synaptic plasticity

that has attracted the interest of scientists working on fragile X and other forms of monogenic autism. Graham is an absolute authority in the field of synaptic plasticity. The authors discuss the role played by the GluA2 subunit of AMPA receptors in mGlu receptor-dependent LTD proposing a molecular model that links functional and structural plasticity through molecular events mediating actin remodeling.

Three chapters by (i) Paolo Gubellini, Yoland Smith, and Marianne Amalric; (ii) Gunasingh Masilamoni and Yoland Smith; and (iii) Nicolas Morin and Therese di Paolo focus on the role played by mGlu5 receptors in the pathophysiology of Parkinson's disease (PD) and L-DOPA-induced dyskinesias (LIDs). These chapters highlight the importance of translation research in the mGlu field describing how data obtained in preclinical models (e.g., 6-hydroxydopamine-treated rats and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated mice and monkeys) laid the groundwork for clinical studies with mGlu5 receptor NAMs in patients with PD and LIDs. Of note, mGlu5 receptor NAMs not only produce symptomatic benefit in PD and LIDs but also exert neuroprotective effects in "parkinsonian" mice and monkeys, suggesting that these drugs cater the potential to behave as disease modifiers.

The chapter by Javier Gonzalez-Maeso is a nice synopsis of the epigenetic and functional mechanisms regulating the cross talk between mGlu2 and 5-HT_{2A} receptors. This mechanism, which has been described in detail in some seminal papers by Javier and his collaborators, is of great relevance to the pathophysiology and treatment of schizophrenia.

The chapter by Francesco Ferraguti focuses on mGlu receptors in the amygdala, a complex brain structure that plays a key role in fear memory and anxiety. Francesco is one of the best neuroanatomists and pharmacologists in Europe, and he is highly contributing to our current knowledge of the complex neuronal circuits linking the input and output nuclei of the amygdaloid complex.

The chapter by Tom Salt and Carolina Copeland examines the role played by mGlu receptors in the regulation of synaptic transmission in the thalamus. Tom Salt's lab is pioneer in the study of thalamic function in response to sensory inputs.

The chapter by Gilles van Luijtelaa, Valerio D'Amore, Ines Santolini, and Richard Ngomba focuses on mGlu5 receptors as a new candidate drug target for the treatment of absence epilepsy. Absence seizures are characterized by spike-and-wave discharges at the EEG, which are generated by an abnormal oscillatory activity within a cortico-thalamic-cortical circuit. A significant percentage of patients with absence epilepsy is refractory to current medication. mGlu5 receptor PAMs hold promise as new drugs for the treatment of absence epilepsy and may act in the thalamus by restraining GABAergic transmission.

The chapter by Francesca Guida, Enza Palazzo, L. Longo, Ida Marabese, Vito de Novellis, and Sabatino Maione examines the role played by mGlu receptors in the pain pathways focusing on supraspinal mechanisms. Supraspinal mechanisms are involved in the top-down regulation of pain transmission and mediate the affective and cognitive aspects of pain, being a linking bridge between chronic pain and affective disorders. Dino Maione's group is leader in the study of mGlu receptors and pain regulation.

The chapter by Andrew Lawrence and Christina Perry focuses on mGlu receptors as candidate drug targets for the treatment of drug addiction. Several lines of evidence indicate that mGlu5 receptor NAMs inhibit both drug taking and drug seeking. Here, the authors comment on mGlu5 receptors and drug addiction from a different angle. Moving from the evidence that mGlu5 receptors contribute to mechanisms of activity-dependent synaptic plasticity, Andrew and Christina suggest that mGlu5 receptor PAMs may serve as useful add-on treatment to behavioral therapy in addiction.

Finally, the chapter by Suzy Chen is a nice synopsis of what we currently know about mGlu receptors and cancer and focuses on the link between mGlu1 receptors and the pathophysiology of malignant melanomas. Melanoma is one of the most aggressive tumors originating from melanocytes, which are cells present in the skin, uvea, and leptomeninges and originate from the neural crest. Although the current use of BRAF and MEK inhibitors and immunotherapies has extended the progression-free survival and overall survival of patients, the treatment of metastatic melanomas is still suboptimal. Suzy Chen and her collaborators have demonstrated that ectopic expression of mGlu1 receptors in melanocytes is sufficient to generate melanomas in mice and that human melanoma samples and melanoma cell lines express mGlu1 receptors. Riluzole, a drug that lowers the concentrations of ambient glutamate, limits the growth of melanomas and shows radio-sensitizing activity in the treatment of brain metastasis of melanoma. This paves the way to the clinical use of drugs that restrain the activation of mGlu1 receptors as adjunctive treatment in patients with melanoma.

In conclusion, this is an excellent book that is easy to read and critically reviews some of the most relevant aspects related to the physiology and pharmacology of mGlu receptors.

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